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MINIATURE PIG PERFORMANCE AFTER FRACTIONATED DOSES OF RADIATION: TIME-DOSE RELATIONSHIPS

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ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Atomic Support Agency
Bethesda, Maryland

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MINIATURE PIG PERFORMANCE AFTER FRACTIONATED DOSES OF RADIATION: TIME-DOSE RELATIONSHIPS

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FOREWORD
(Nontechnical summary)

Previous studies have shown that the responses of the rhesus monkey and miniature pig to supralethal doses of radiation are reduced when such doses are fractionated.

When 6800- to 13,300-rad midline tissue doses of mixed gamma-neutron radiation were given in two equal fractions 5 hours apart, the postirradiation performance of miniature pigs was much better than when the radiation was delivered in equivalent single uninterrupted doses. Furthermore, the postirradiation performance of the miniature pigs tended to be better after the second than after the first fraction of the fractionated dose. Survival times also increased when the doses were fractionated.

The objectives of this study were to determine if the response of miniature pigs after a dose given in two fractions was dependent upon either the interval between fractions or the size of the first fraction.

Six groups of miniature pigs received a 4400-rad midline tissue dose of pulsed mixed gamma-neutron radiation followed 1/2, 1, 5, 15, 24, or 51 hours later by a second dose of equivalent magnitude. Two other groups of pigs were given a lower initial dose (1700 or 3400 rads) followed 1 hour later by a dose of 4800 to 5000 rads. In addition two groups of pigs received unfractionated doses of either 4500 or 8600 rads.

Before irradiation the pigs were trained to traverse a shuttlebox when presented with visual and auditory cues. Their postirradiation performance was tested at specified intervals until death.

Regardless of the time interval between the two 4400-rad doses, performance was generally better after the second dose than after the first. Early transient incapacitation accompanied always by convulsions, and occasionally by coma, consistently occurred after the first dose but was infrequent after the second. When early transient incapacitation did occur after the second dose, it was generally shorter than after the first dose and accompanied by ataxia and disorientation; convulsions and coma were very infrequent.

As expected, performance after the first of two 4400-rad doses was significantly better than after a single 8600-rad dose. But, because of the reduced response to the second 4400-rad dose, performance after an 8800-rad fractionated dose was markedly better than after an 8600-rad unfractionated dose.

No early transient incapacitation occurred after the second of two 4400-rad doses 1 hour apart. As the first dose was reduced to 3400 or to 1700 rads, early transient incapacitation, accompanied by occasional convulsions, was observed after the subsequent 4800- to 5000-rad dose. Furthermore, early transient incapacitation was longer and was more frequently accompanied by convulsions when the initial dose was only 1700 rads.

Mean survival times of all groups of pigs receiving fractionated doses were similar to that of pigs receiving a single 4500-rad dose and significantly longer than that of pigs receiving a single 8600-rad dose.

ABSTRACT

Miniature pigs were trained to traverse, on cue, a two-chambered shuttlebox. Six groups of five to eight pigs received a 4400-rad midline tissue dose of pulsed mixed gamma-neutron radiation followed 1/2, 1, 5, 15, 24, or 51 hours later by a second dose of equivalent magnitude. Two other groups of eight pigs received a lower initial dose (1700 or 3400 rads) followed 1 hour later by a second dose of 4800 to 5000 rads. In addition, unfractionated doses of either 4500 or 8600 rads were given to two groups of six pigs. Regardless of the time interval between the two 4400-rad doses, performance was generally better after the second dose than after the first. Early transient incapacitation, accompanied always by convulsions, and occasionally by coma, consistently occurred after the first dose but was infrequent after the second. When early transient incapacitation did occur after the second dose, it was generally shorter than after the first dose and accompanied by ataxia and disorientation; convulsions and coma were very infrequent. Because of this reduced response to the second 4400-rad dose, performance after an 8800-rad fractionated dose was markedly better than after an 8600-rad unfractionated dose. However, as the first dose was reduced to 3400 or 1700 rads, early transient incapacitation accompanied by occasional convulsions was observed after the subsequent 4800- to 5000-rad dose. Furthermore, early transient incapacitation was longer and was more frequently accompanied by convulsions when the initial dose was only 1700 rads. Mean survival times of all groups of pigs receiving fractionated doses were similar to that of pigs receiving a single 4500-rad dose and significantly longer than that of pigs receiving a single 8600-rad dose.

I. INTRODUCTION

Previous studies have shown that the responses of the rhesus monkey and miniature pig to supralethal doses of radiation are reduced when such doses are fractionated.[1,3]

When 6800- to 13,300-rad midline tissue doses of pulsed mixed gamma-neutron radiation were given in two equal fractions, 5 hours apart, the postirradiation performance of miniature pigs was much better than when the radiation was delivered in single uninterrupted doses. Furthermore, the performance of the miniature pigs tended to be better after the second than after the first fraction of the fractionated dose. Survival times also increased when the doses were fractionated.

The objectives of this study were to determine how the responses of miniature pigs after a dose given in two fractions depended upon the interval between fractions and upon the size of the first fraction.

II. PROCEDURES

The subjects were 68 miniature pigs (males, females, and barrows) of the Hormel and Hormel-Hanford strains. When irradiated the animals were 4 to 6 months old, weighed 20 to 35 kg and were 17 to 20 cm thick at the shoulders.

Each pig was exposed unilaterally to the left side to one or two pulses of gamma-neutron radiation from the AFRRI-TRIGA reactor.[5] The midline of all animals was about 100 cm from the vertical center line of the reactor core. The exposure configuration has been previously described.[1,2] All doses reported are to the midline of the trunk of the pig and were calculated by previously reported methods. The ratio of head to trunk midline tissue dose was approximately 1.5. Since the ratio of

maximum to minimum dose exceeded 1.3, the irradiations were Class B nonuniform as defined in the International Commission on Radiological Units and Measurements Report 10e.

Six groups of five to eight pigs received an initial dose of 4400 rads followed 1/2, 1, 5, 15, 24, or 51 hours later by a second dose of equivalent size. Two other groups of eight pigs were given a lower initial dose (1700 or 3400 rads) followed 1 hour later by a dose of 4800 to 5000 rads. In addition, unfractionated doses of either 4500 or 8600 rads were given to two groups of six pigs.

All pigs were trained by shock avoidance conditioning to traverse a two-chambered shuttlebox as described in previous studies.[1,2] During each trial the pig had 6 seconds to avoid electrical shock by crossing the shuttlebox while visual and auditory cues were presented, 4 seconds to escape electrical shock by crossing after the shock was initiated, and 3 seconds to rest. Before irradiation each pig was trained to a minimum performance criterion of 90 percent avoidance. Each postirradiation test consisted of 10 trials.

Pigs that received unfractionated doses were released into the shuttlebox immediately after irradiation and tested at 0, 2-1/2, 5, 7-1/2, 10, 15, 20, 25, 30, and 45 minutes, at each hour until 4 hours postirradiation, and then at 2-hour intervals until death. The pigs that received fractionated doses were tested on the same schedule until returned to the exposure box 30 minutes prior to reirradiation. After the second dose fraction, animals were tested on the same schedule starting again at time zero and ending at death. The limited time between the two doses given only 1/2 hour apart did not allow for testing between dose fractions. These animals were not

released from the exposure box until after the second dose fraction had been delivered. A pig was scored incapacitated when it did not cross the shuttlebox in two or more consecutive trials. A proficiency of 90 percent avoidance was required for acceptable performance.

Performance differences were evaluated with the Wilcoxon matched-pairs signed-ranks test or the chi-square test for independent samples. Survival time differences were evaluated with Student's "t" test. Results were considered significantly different when $P \leq 0.05$.

III. RESULTS*

Duration of early transient incapacitation (ETI), onset of acceptable performance, and the number of avoidances achieved during the first 30 minutes postirradiation are presented in Table I for pigs which received an initial dose of 4400 rads followed 1/2, 1, 5, 15, 24, or 51 hours later by a second dose of equivalent size. Data are also given for the animals which received a single 8600-rad dose. Postirradiation performances for these groups of animals are summarized in Figures 1-3. Survival time data are presented in Table II.

Regardless of the time interval between the two 4400-rad doses, performance after the second dose was not significantly different (15-hour group) or was significantly better (all other groups except the 1/2-hour group which was not tested between doses)

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* Five pigs were permanently incapacitated immediately after a single 4400-rad pulsed dose of mixed gamma-neutron radiation. Three died before they could be reirradiated (two in the 1-hour and one in the 24-hour groups) and are included only in survival time data shown in Table II. Two died shortly after the second 4400-rad dose (one in the 1-hour and one in the 15-hour groups) and are included in the data shown in Table I but not in Figures 1 and 2.

Table I. Miniature Pig Performance after Fractionated and Unfractionated Doses of Radiation: Effects of Changes in Time Interval between Two 4400-Rad Dose Fractions

Pig #	Fractionated dose (4400 + 4400 rads)						
	Time between fractions (h)	Duration of ETI (min)		Onset of acceptable* performance (min postirradiation)		Number of avoidances during first 30 min (90 possible)	
		Fraction 1	Fraction 2	Fraction 1	Fraction 2	Fraction 1	Fraction 2
1	1/2	†	3.5‡	†	10	†	56
2		†	0	†	7.5	†	81
3		†	0	†	0	†	85
4		†	0	†	2.5	†	80
5		†	0	†	25	†	57
6		†	0	†	2.5	†	85
7	1	9.7	0	15	0	44	90
8		16.3	0	20	7.5	29	82
9		1.3	0	10	0	73	85
10		2.5	0	10	0	68	87
11		1.5	0	7.5	0	78	90
12		1.2	0	10	0	65	84
13		§	§	§	§	0	0
14	5	1	1	10	5	74	76
15		0	0	10	10	73	79
16		22	5	25	15	19	63
17		1	0	10	5	78	85
18		0	0	5	0	84	86
19		0	0	7.5	5	73	83
20	15	0	0	0	5	89	83
21		0	0	0	10	88	81
22		17	0	20	2.5	28	83
23		15	30‡	25	**	32	7
24		1.4	0	5	5	80	85
25		12.1	0	25	5	35	80
26		15	0	20	10	36	75
27		§	§	§	§	0	0
28	24	6	0	10	5	54	85
29		9	0	15	0	49	90
30		2	0	7.5	0	72	87
31		30.5	0	45	5	8	78
32		12	0	20	5	38	86
33	51	11	3.9‡	20	7.5	38	66
34		8.8	5‡	20	5	56	68
35		31.5	10.8	90	30	3	37
36		1.3	2.1‡	10	2.5	68	76
37		15.2	0.5‡	25	5	30	81
	Unfractionated dose (8600 rads)						
38		9		20		38	
39		30		120		4	
40		40		**		0	
41		240		**		0	
42		10		15		43	
43		60		**		0	

* Proficiency of 90 percent avoidance
† Pigs were not tested between fractions 1 and 2
‡ No convulsions were observed during ETI
§ Permanently incapacitated immediately postirradiation
** Between ETI and permanent incapacitation, pig never achieved acceptable performance

Table II. Miniature Pig Survival Time after Fractionated and Unfractionated Doses of Radiation*

Fractionated Dose								
Size of dose fractions (rads)	4400 + 4400						1700 + 4800	3400 + 5000
Hours between fractions	1/2	1	5	15	24	51	1	1
Survival time (h)	Number of pigs (mean survival time)							
<2	1(1.25)	3†(0.5)			1†(0.1)			
8-39				2(22)	1(38)			
40-118	5(85)	6(69)	6(90)	6(56)	4(75)	5(77)	8(70)	8(54)

Unfractionated dose			
Size of dose (rads)	4500	8600	
Survival time (h)	Number of pigs (mean survival time)		
<2	1(0.1)	1(1.5)	
8-39		4(25)	
40-118	5(71)	1(71)	

* Calculated from the initial dose

† Two pigs in the 1-hour and one pig in the 24-hour groups died before the second 4400-rad dose was delivered

than after the first dose. ETI, accompanied always by convulsions and occasionally by coma, consistently occurred after the first dose but was infrequent after the second. When ETI did occur after the second dose, it was generally shorter than after the first dose and accompanied by ataxia and disorientation; convulsions and coma were very infrequent. Furthermore, ETI was followed by a more rapid recovery to an acceptable level of performance after the second dose than after the first dose.

Miniature pig performance after fractionated 8800-rad doses was significantly better than after unfractionated 8600-rad doses (Table I). ETI occurred less often, and when it did occur, was much shorter and was followed by a more rapid recovery to acceptable performance levels. Since the animals usually performed at acceptable levels until they became permanently incapacitated several hours before death, the duration of acceptable performance paralleled survival time.

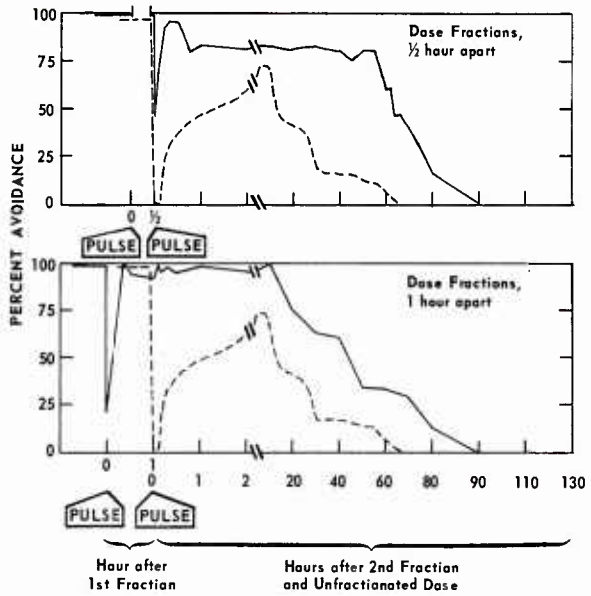

Figure 1. Average avoidance response of miniature pigs after two 4400-rad doses, 1/2 and 1 hour apart, and after a single 8600-rad dose of radiation. The curves in each dose group represent the average performance of six pigs.
Unfractionated dose ----- Fractionated dose ——

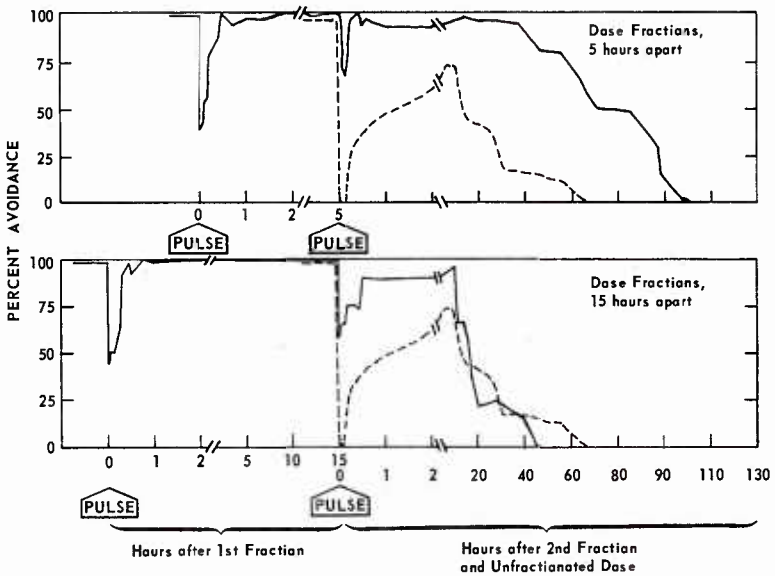

Figure 2. Average avoidance response of miniature pigs after two 4400-rad doses, 5 and 15 hours apart, and after a single 8600-rad dose of radiation. The curves in each dose group represent the average performance of six or seven pigs.
Unfractionated dose ----- Fractionated dose ——

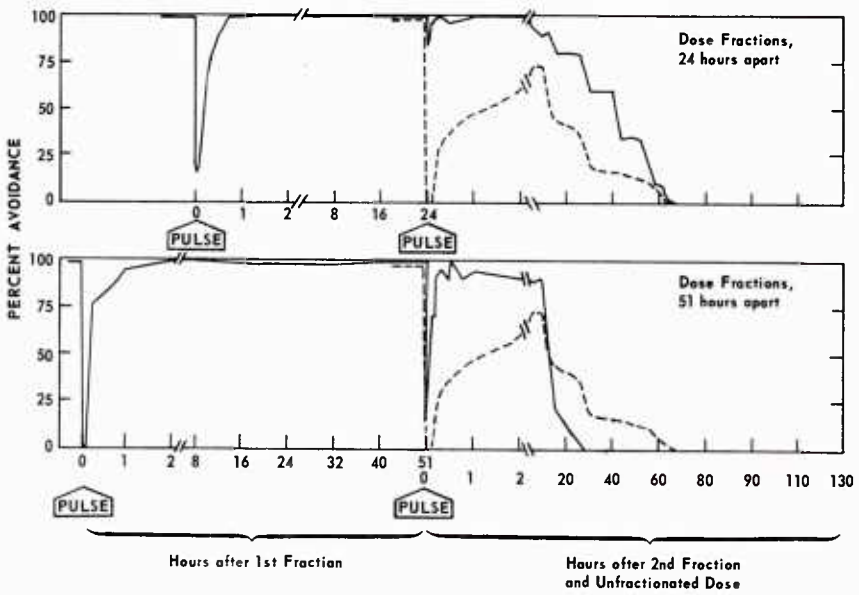

Figure 3. Average avoidance response of miniature pigs after two 4400-rad doses, 24 and 51 hours apart, and after a single 8600-rad dose of radiation. The curves in each dose group represent the average performance of five or six pigs. Unfractionated dose ----- Fractionated dose ——

Mean survival times of all groups of pigs receiving fractionated doses (calculated from the initial dose fraction) were similar to that of pigs receiving a single 4500-rad dose and significantly longer than that of pigs receiving a single 8600-rad dose.

Miniature pig performance and survival time after fractionated doses consisting of different initial doses followed 1 hour later by similar second doses (1700 + 4800, 3400 + 5000, and 4400 + 4400 rads) are shown in Tables II and III. Performance after the second dose was poor when the initial dose was 1700 rads, showed a significant improvement when the initial dose was increased to 3400 rads, and was markedly better when the initial dose was 4400 rads. No ETI or convulsions were observed after pigs received the second of two 4400-rad doses. When the initial

dose was reduced to 3400 or to 1700 rads, nearly all animals suffered ETI, with some animals convulsing, after the second dose. Furthermore, ETI after the second dose was longer and was always accompanied by severe convulsions when the initial dose was only 1700 rads. In spite of different total doses (6500, 8400, and 8800 rads) survival time did not differ significantly among the three groups.

Table III. Miniature Pig Performance after Fractionated Doses of Radiation: Effects of Changes in Size of First Dose Fractions

Pig #	Duration of ETI (min)		Onset of acceptable* performance (min postirradiation)		Number of avoidances during first 30 min (90 possible)	
	Fraction 1	Fraction 2	Fraction 1	Fraction 2	Fraction 1	Fraction 2
1700 + 4800 rads, 1 hour apart						
44	0	30	0	45	88	0
45	0	16.2	0	20	87	31
46	0	11.5	0	15	89	43
47	0	15.3	0	30	88	28
48	0	0	0	0	88	88
49	0	45	7.5	60	83	0
50	0	15	5	15	74	38
51	0	1.2	0	10	90	68
3400 + 5000 rads, 1 hour apart						
52	15.3	1.3	20	10	38	68
53	>30	†	>30	†	0	†
54	7.5	1.6	7.5	2.5	61	81
55	1.7	0.7	2.5	2.5	80	85
56	1.6	1.8	7.5	10	74	86
57	1.5	30	2.5	45	84	5
58	8	0.5‡	15	30	56	69
59	5.8	15.7‡	15	20	40	34
4400 + 4400 rads, 1 hour apart						
7	9.7	0	15	0	44	90
8	16.3	0	20	7.5	29	82
9	1.3	0	10	0	73	85
10	2.5	0	10	0	68	87
11	1.5	0	7.5	0	78	90
12	1.2	0	10	0	65	84
13	§	§	§	§	0	0

* Proficiency of 90 percent avoidance

† Equipment malfunction; animal performed at acceptable level when first tested at 11.5 minutes postirradiation.

‡ No convulsions were observed during ETI

§ Permanently incapacitated immediately postirradiation

IV. DISCUSSION

Although the interval between the two halves of 8800-rad fractionated doses was varied from 1/2 to 51 hours, overall performance after the second half of these doses was generally better than after the first half. In addition, performance after the fractionated 8800-rad dose was markedly better than after an equivalent unfractionated dose. It appears that, within the limits of 1/2 to 51 hours, the response of miniature pigs to a supralethal dose delivered in two equal fractions is independent of the interval between the dose fractions.

In contrast, however, the response of miniature pigs after the fractionated dose was dependent upon the size of the initial dose. As the initial dose was reduced to 3400 and finally to 1700 rads, responses of the animals to a subsequent 4800- to 5000-rad dose became more severe. Previous results suggest that miniature pig performance after two 3400-rad doses was less effective than after two 4250-rad or even two 5500-rad doses.[1] Therefore, the data from both studies indicate that an initial dose of at least 4000 rads is required before the pigs become relatively insensitive to additional radiation, and that a lower dose of 3400 rads is only partially effective in reducing the response of the animals to a second supralethal dose. Finally an initial dose of only 1700 rads appears to enhance the effectiveness of a second supralethal dose.

Although the duration of ETI was shorter than after the initial dose, pigs were severely affected after receiving the second of two 6600-rad doses.[1] It is evident that dose fractionation was much less effective in reducing the response of pigs to this

higher total dose of radiation (13,000 rads) than it was at lower supralethal doses. It is suggested, therefore, that, regardless of dose fractionation, overall pig performance rapidly deteriorates as the total dose approaches 13,000 to 14,000 rads. It is quite possible that this upper limit is independent of either the first or second dose size.

Most miniature pigs receiving unfractionated 5000-rad or greater doses of mixed gamma-neutron radiation were incapacitated with severe convulsions and frequently coma within seconds after irradiation.[2] The most striking result obtained in the current study was the virtual absence of convulsions after the second of two 4400-rad doses (fractionated 8800-rad dose). Although some animals suffered ETI after these fractionated doses the clinical symptoms were almost exclusively ataxia and disorientation.

It has been previously reported that 500 to 10,000 R x-ray exposures decreased the electroshock seizure threshold of rats below that of unirradiated animals.[4,6-8] In spite of this reduced seizure threshold, however, the intensity of electroshock-induced convulsions also decreased after 5000 to 10,000 R.[4,8] This reduced seizure intensity was interpreted as a decreased capacity for sustained heightened nervous activity by the brain after these higher doses of radiation.[8]

It is suggested that the pig's response has some similarities to that of the rat. Supralethal doses probably reduce the seizure threshold and thus heighten the susceptibility of pigs to the convulsive effect of later doses of radiation. The tendency towards more severe convulsions after the second dose when the initial dose was only 1700 rads could be indicative of a reduced seizure threshold. With increasing initial

doses, the lower incidence of convulsions after the second dose could be accounted for by the reduced ability of the brain to sustain the heightened nervous activity necessary to maintain convulsions.

Mean survival time after the second dose fraction became progressively shorter as the time interval between doses was increased from 1/2 to 51 hours. However, when calculated from the initial dose fraction, survival time did not differ significantly among the groups. Therefore, since the second 4400-rad dose appeared to have little additional effect on survival time, it is reported as the time from the initial dose until death.

The data obtained from these studies on miniature pig performance after fractionated and unfractionated doses of pulsed mixed gamma-neutron radiation allow the following conclusions to be drawn.

1. Miniature pigs perform much better after receiving 6800- to 13,300-rad doses in two equal fractions than after equivalent unfractionated doses.

2. Miniature pig performance is generally better after the second half than after the first half of a fractionated dose.

3. For a fractionated 8800-rad dose, the response is not affected by changing the time interval between the two equal dose fractions over the range of 1/2 to 51 hours. This probably applies regardless of dose size.

4. Initial doses below 4000 rads are less effective in reducing the response of pigs to a subsequent supralethal dose than are doses above 4000 rads. Initial doses of approximately 1500 rads may actually result in a greater response to subsequent supralethal doses than would occur had the animals been previously unirradiated.

5. Whether the dose is fractionated or delivered in a single pulse, miniature pig performance rapidly deteriorates as the total dose approaches 13,000 to 14,000 rads.

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13. ABSTRACT

Miniature pigs were trained to traverse, on cue, a two-chambered shuttlebox. Six groups of five to eight pigs received a 4400-rad midline tissue dose of pulsed mixed gamma-neutron radiation followed 1/2, 1, 5, 15, 24, or 51 hours later by a second dose of equivalent magnitude. Two other groups of eight pigs received a lower initial dose (1700 or 3400 rads) followed 1 hour later by a second dose of 4800 to 5000 rads. In addition, unfractionated doses of either 4500 or 8600 rads were given to two groups of six pigs. Regardless of the time interval between the two 4400-rad doses, performance was generally better after the second dose than after the first. Early transient incapacitation, accompanied always by convulsions, and occasionally by coma, consistently occurred after the first dose but was infrequent after the second. When early transient incapacitation did occur after the second dose, it was generally shorter than after the first dose and accompanied by ataxia and disorientation; convulsions and coma were very infrequent. Because of this reduced response to the second 4400-rad dose, performance after an 8800-rad fractionated dose was markedly better than after an 8600-rad unfractionated dose. However, as the first dose was reduced to 3400 or 1700 rads, early transient incapacitation accompanied by occasional convulsions was observed after the subsequent 4800- to 5000-rad dose. Furthermore, early transient incapacitation was longer and was more frequently accompanied by convulsions when the initial dose was only 1700 rads. Mean survival times of all groups of pigs receiving fractionated doses were similar to that of pigs receiving a single 4500-rad dose and significantly longer than that of pigs receiving a single 8600-rad dose.